QUANTITATIVE INDICIES OF
THE SHOCK SYNDROME

PROGRESS REPORT

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July 1, 1970 - May 1, 1971

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ABSTRACT

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The present studies demonstrate the usefulness of routine measurements of plasma c.o.p. both as a prognostic index of the course of the shock syndrome and as a guide for the effectiveness of other therapeutic measures. Severe and protracted hemorrhagic shock is associated with a failure of hemodilution mechanisms and a trend for $P\ell_\pi$ and blood hematocrit to become dissociated. Endotoxin has a clear cut action on neurogenic readjustment mechanisms which is masked in anesthetized animals. Survivors of an LD/50 dose of endotoxin show a blunting of compensatory constrictor responses and, thereby, permit peripheral blood flow to be maintained more effectively as cardiac output and central pressure fall. Measurements of pressure within the microcirculation reveal that fatal shock is associated with an inability to maintain P_c and a progressive narrowing of the pressure differential or hydraulic driving force across the capillary bed. Fluid exchange at the capillary level is disrupted when P_c and $P\ell_\pi$ are no longer in balance and lead to extensive venular stasis during shock. Electrolyte therapy in hemorrhagic shock becomes less effective as the capillary barrier begins to show evidence of increased permeability (filtration coefficients may increase 2 to 3 fold).

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13. ABSTRACT

1. The present studies demonstrate the usefulness of routine measurements of plasma c.o.p. both as a prognostic index of the course of the shock syndrome and as a guide for the effectiveness of other therapeutic measures.
2. Severe and protracted hemorrhagic shock is associated with a failure of hemodilution mechanisms and a trend for P_π^ℓ and blood hematocrit to become dissociated.
3. Endotoxin has a clear-cut action on neurogenic readjustment mechanisms which is masked in anesthetized animals.
4. Survivors of an LD/50 dose of endotoxin, show a blunting of compensatory constrictor responses and thereby permit peripheral blood flow to be maintained more effectively as cardiac output and central pressure fall.
5. Measurements of pressure within the microcirculation reveal that fatal shock is associated with an inability to maintain P_c and a progressive narrowing of the pressure differential or hydraulic driving force across the capillary bed.
6. Fluid exchange at the capillary level is disrupted when P_c and P_π^ℓ are no longer in balance and lead to extensive venular stasis during shock.
7. Electrolyte therapy in hemorrhagic shock becomes less effective as the capillary barrier begins to show evidence of increased permeability (filtration coefficients may increase 2 to 3 fold).

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	ROLE	WT	ROLE	WT	ROLE	WT
Colloid osmotic pressure						
Blood						
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Shock						
Endotoxin shock						
Baroreceptors and endotoxin						
Capillary permeability, hemorrhage						
Electrolyte therapy, hemorrhage						

FORWORD

In conducting the research described in this report, the investigators
adhered to the "Guide for Laboratory Animal Facilities and Care,"
as promulgated by the Committee on the Guide for Laboratory Animal,
Resources, National Academy of Sciences-National Research Council.

PROGRESS REPORT

July 1, 1970 - May 1, 1971

Our research on experimental shock during the past year is discussed under four categories:

1. Blood colloid osmotic pressure as a prognostic index during shock.

2. Neurogenic adjustments in endotoxic shock.

3. Pressure gradients in the microvasculature during hemorrhagic shock.

4. The blood-tissue barrier following hemorrhage.

1. Measurement of Blood Colloid Osmotic Pressure.

A need exists to define the parameters best suited to assess the status of the shock patient undergoing therapy. For the most part, systemic pressure and related variables are used, but they have not been found to be reliable indicies of peripheral vascular insufficiency. A major objective has, therefore, been to develop clinical indicies which reflect vascular function at the tissue level. The inaccessibility of the microvasculature and the complexity of quantitative measurements of small vessel dynamics have made it impractical to obtain such direct information on a routine basis.

Under steady-state conditions the blood leaving the tissue should be in osmotic balance with arterial blood except for metabolic reactants and relative gas tensions. Two approaches were used to detect disturbances of the tissue level which normally ensure fluid balance. The first was the development of a suitable membrane osmometer for measuring accurately and rapidly the colloid osmotic pressure of blood samples. A second was the measurement of the electrical conductivity of venous blood under conditions which reflected changes in hematocrit and plasma protein concentration. Although the latter was not directly applicable to clinical shock, it was hoped that a mathematical

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relationship could be established on the experimental level that would permit its application to the problem in man.

Membrane osmometers have been used for the measurement of colloid osmotic pressure of physiological fluids, but they have been slow, technically difficult to handle and not sufficiently accurate to be used on a routine basis. For the past two years we have devoted much time to this problem and on the basis of our laboratory experience have gradually modified such units to make them applicable to the needs of the shock problem. Factors such as the type of membrane, the mounting receptacle, type of transducer for measuring pressure, temperature control, etc. have been investigated and at the laboratory level two workable models have been developed and are in use on a routine basis. Plasma or whole blood osmotic pressure can be determined in five minutes. We feel confident that the unit can be further miniaturized and made into a practical clinical instrument.

Routine measurements have been made of serial blood samples drawn during hemorrhagic hypotension and endotoxemia in rabbits, and dogs. As previously reported, there is considerable variability in control levels of plasma c.o.p. ($P\ell_\pi$) of different individuals. Hemorrhage is accompanied by a significant fall in $P\ell_\pi$, to as much as 50-60% below control levels. In those cases where fatal shock develops, $P\ell_\pi$ then begins to increase and the trend continues until death. This shift occurs independently of the hematocrit. In fact, the two indicies may show opposite trends during profound hypotension. The prognostic value of the $P\ell_\pi$ trend was clearly established when reversible and irreversible forms of hemorrhagic shock were compared. Survivors uniformly continued to maintain the compensatory hemodiluted level achieved early and showed only a modest reversal after 4-5 hours of hypotension.

Endotoxic shock was studied primarily in rabbits. Animals given a

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lethal dose of E. coli or S. enteritidis endotoxin showed no hemodilution, only a continuous trend towards elevated Pl_π values which appeared several hours after administration of these extracts. Those animals which survived longest showed the smallest perturbation in plasma colloid osmotic pressure.

In practice, measurements of the plasma samples were made on a conventional strip chart recorder and it was found that plasma from individuals in shock presented an unusual pattern which we have interpreted to indicate the presence of considerable amounts of newly formed low molecular weight materials in the blood. These materials presumably have a molecular weight of several thousand and could be fractionated by using membranes of different porosity. Examples of such tracings are shown in the accompanying figure (#1) of successive samples taken over a four hour period during the development of fatal hemorrhagic hypotension. The spike which appears immediately indicates a rapid diffusion of osmotically active material out of the test chamber.

Experiments were also carried out in partially eviscerated (stomach and duodenum intact) and in completely eviscerated dogs and rabbits. Significantly, the fall in Pl_π associated with compensatory hemodilution was almost absent in eviscerate preparations subjected to hemorrhage. It has been assumed that most of the fluid drawn into the vascular system during hemo-dilution comes from the skeletal muscle mass. The Pl_π levels in eviscerate animals remained essentially unchanged until approximately 60 minutes before death when the Pl_π values began to rise, as in sham operated controls subjected to similar hemorrhage.

HEMORRHAGIC SHOCK
RABBIT
March 25, 1970

SAMPLE #10   C.O.P. 24.0 cm H_2O

SAMPLE #9   C.O.P. 22.8 cm H_2O

SAMPLE #5   C.O.P. 22.8 cm H_2O

SAMPLE #2   C.O.P. 23.2 cm H_2O

SAMPLE #1   C.O.P. 25.2 cm H_2O

CONTROL
C.O.P. 24.0 cm H_2O

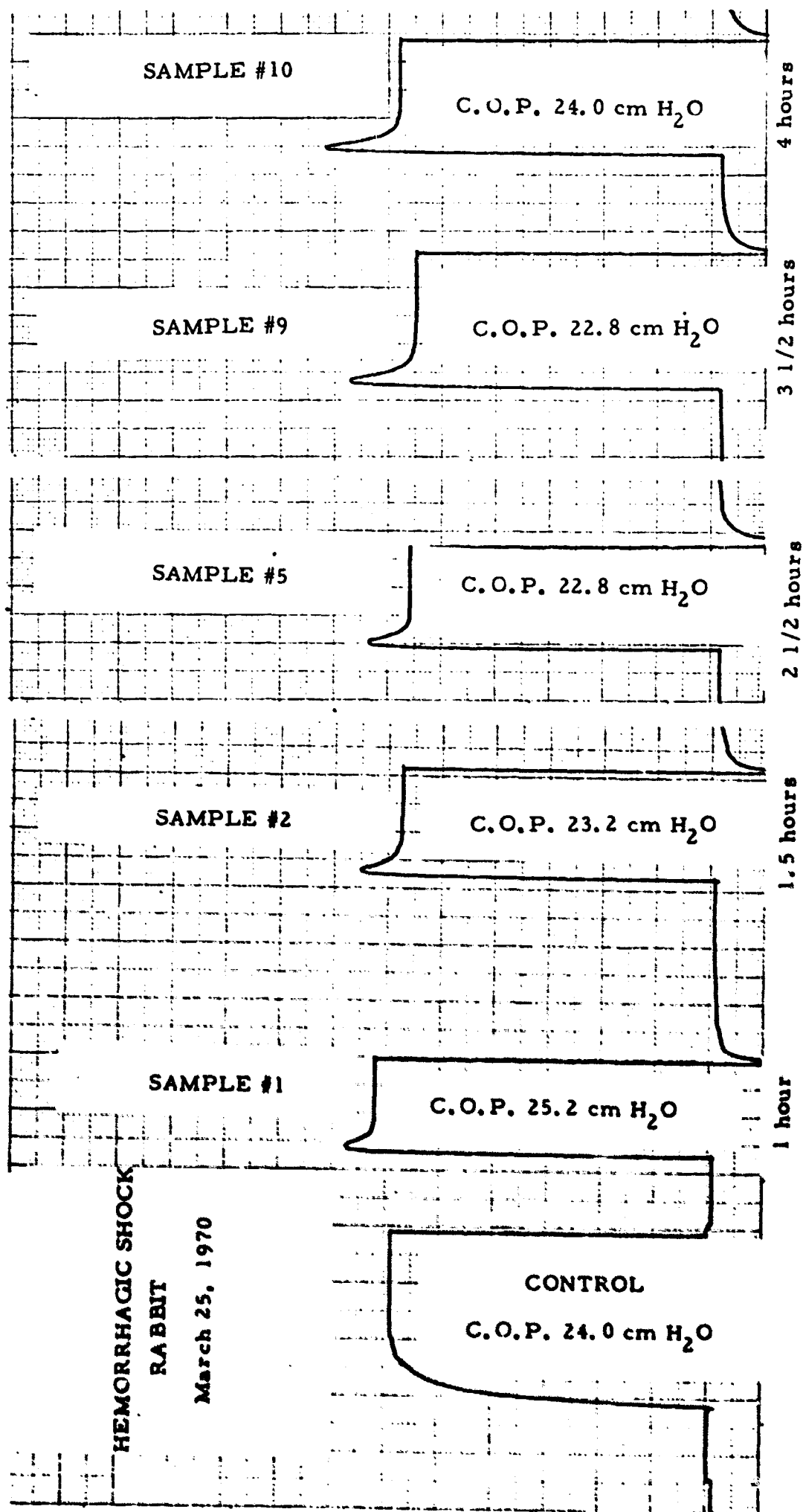4 hours   3 1/2 hours   2 1/2 hours   1.5 hours   1 hour

Figure 1.

2. Compensatory Readjustments During Endotoxic Shock.

There is no clear indication of the mechanism by which bacterial endotoxins produce a state of circulatory collapse in animals, a syndrome not unlike septic shock in man. There is no clear-cut information concerning the extent to which infectious agents affect the nervous system. Recent studies suggest that some of the uncertainty in the literature can be ascribed to the fact that the systemic effects of endotoxins have been studied for the most part in animals under the influence of general anesthesia. It is well-known that anesthetic agents, in particular the commonly used barbiturates, tend to depress reflex responses and to affect cardiovascular functions.

During the past year we undertook a systematic survey of the overall response to lethal doses of bacterial endotoxins under two sets of experimental conditions. We compared the cardiovascular responses of anesthetized animals with those of non-anesthetized rabbits under identical conditions.

A total of 41 rabbits were divided into two groups: (A) anesthetized (pentobarbital), and (B) conscious animals with chronically implanted catheters and flowmeters. In both groups the same parameters were measured; cardiac output and flow in the superior mesenteric artery [SMA] by implanted electromagnetic probes around the aorta and the superior mesenteric artery respectively. In addition, implanted catheters were used to monitor systemic arterial blood pressure and right atrial pressure. The measuring devices were introduced in group A acutely under barbiturate anesthesia, and in group B following a two-stage sterile surgical implantation one and two weeks before the actual experiment.

Lethal amounts of LPS extracts of E. coli, and S. enteritidis were administered. The dosage was between 1.5 and 2 mg/Kg. There was a considerable scatter in the survival time for both groups, but anesthetized animals

were clearly more susceptible and succumbed earlier following a given dose of endotoxin.

Eight animals under barbiturate anesthesia survived only 3 to 3 1/2 hours post-endotoxin. Their course was characterized by a profound depression of all cardiovascular parameters. A second group of 7 animals survived somewhat longer - at least 5-6 hours post-endotoxin. These two groups are compared in Figure 2. As in rapidly fatal endotoxemia, blood pressure, cardiac output and SMAQ declined progressively but to a lesser degree. The total peripheral resistance (TPR) rose, whereas mesenteric regional resistance (MRR) showed a biphasic course. At first MRR tended to decrease, but some 2 1/2 hour post-endotoxin it began to increase. Atrial pressure fell throughout the experiment but did not become positive until immediately before death.

Inasmuch as prolonged barbiturate anesthesia by itself depresses blood pressure and cardiac output, we concluded that endotoxemia when combined with surgical levels of anesthesia serves to accelerate the general decline of cardiovascular functions.

In the absence of anesthesia, it was possible to recognize three distinct types of cardiovascular adjustments to the selected doses of endotoxin. The 3 categories are associated with different survival times.

In Figure 3, we have listed 7 animals which rapidly developed signs of cardiovascular failure and survived only 3 - 3 1/2 hours post-endotoxin. Despite the rapid decline in cardiac output, TPR did not increase. The associated decompensatory trend of SMAQ and MRR led us to conclude that splanchnic blood pooling in conjunction with a progressively decreasing venous return were responsible for the rapid deteriorization of the circulation in such acute deaths.

A second group of animals survived some 5-6 hours. A summary of the data from 8 rabbits in this category is given in Figure 4. In these animals

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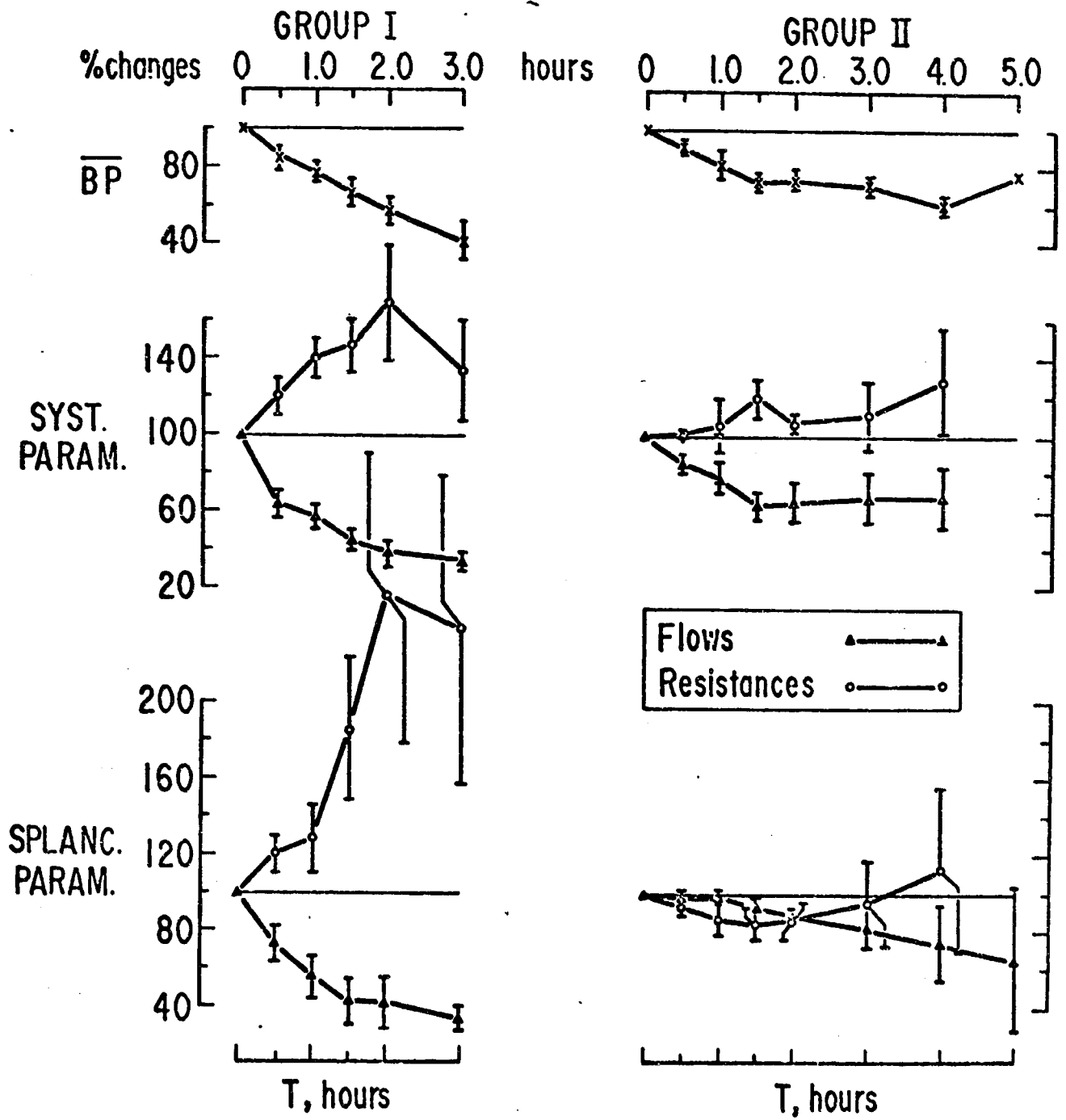# HEMODYNAMIC CHANGES UNDER ANESTHESIA

Figure 2.

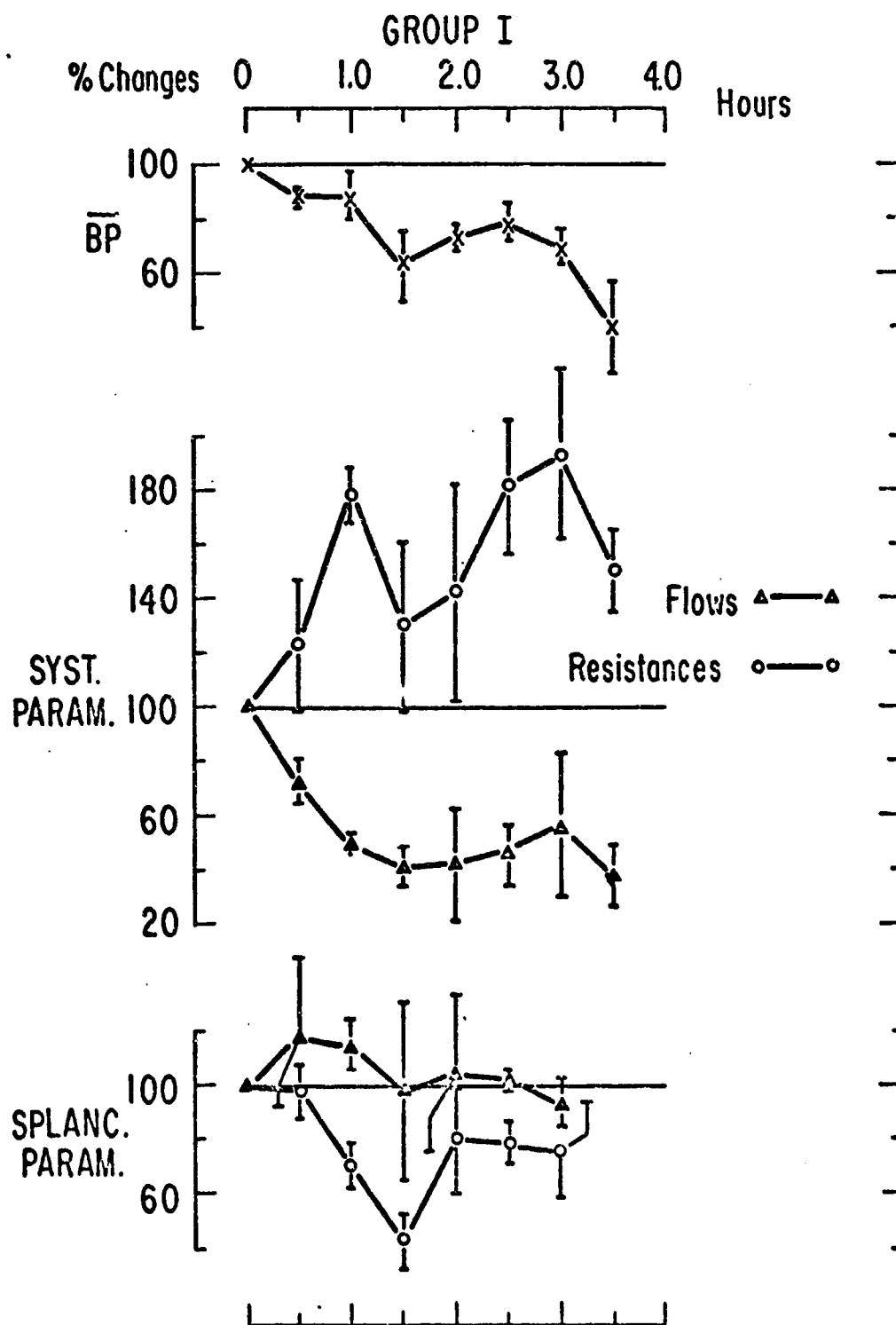# HEMODYNAMIC CHANGES NON-ANESTHETIZED RABBITS

Figure 3.

the resulting decrease in blood pressure, flow (CO) and SMAQ) was accompanied by compensatory adjustments, as reflected by the increase in corresponding resistances. These adjustments were sufficient to increase the survival time, but apparently in time the protracted reduction in blood flow to different parts of the body resulted in circulatory insufficiency. The onset of failure appeared rapidly, usually about 20-30 minutes before death.

Included in Figure 4 is the data for a group of 7 rabbits which survived for at least 8-9 hours following a similar dose of endotoxin. In general, it can be seen that the progressive fall in blood pressure and cardiac output was not accompanied by a proportionate increase in TPR and MRR when compared to the previous group. Despite the fact that this type of readjustment, presumed to be compensatory, is almost completely absent, these animals showed the longest survival time. Under most experimental conditions, even a modest hypotension serves to trigger (presumably via the baroreceptors) an increase of the sympathetic discharge to the heart and peripheral vessels.

In order to come to grips with this apparent inconsistency, we made a study of the sensitivity of the baroreceptor reflex by analyzing the decrease in heart rate which could be induced by a transient increase of the arterial blood pressure. In a recent report by Pickering and co-workers (1970), it was shown that under normal conditions a linear relationship exists between the increase in blood pressure induced by a small amount of Angiotensin I and the ensuing decrease in heart rate. An example of such a relationship is shown in Figure 5. The slope of the line shown is in effect a measure of the baroreceptor response.

This method was used to test the sensitivity of baroreceptors responses in the two groups of the endotoxin-treated animals described previously. The upper part of Figure 6 illustrates the blood pressure levels and the
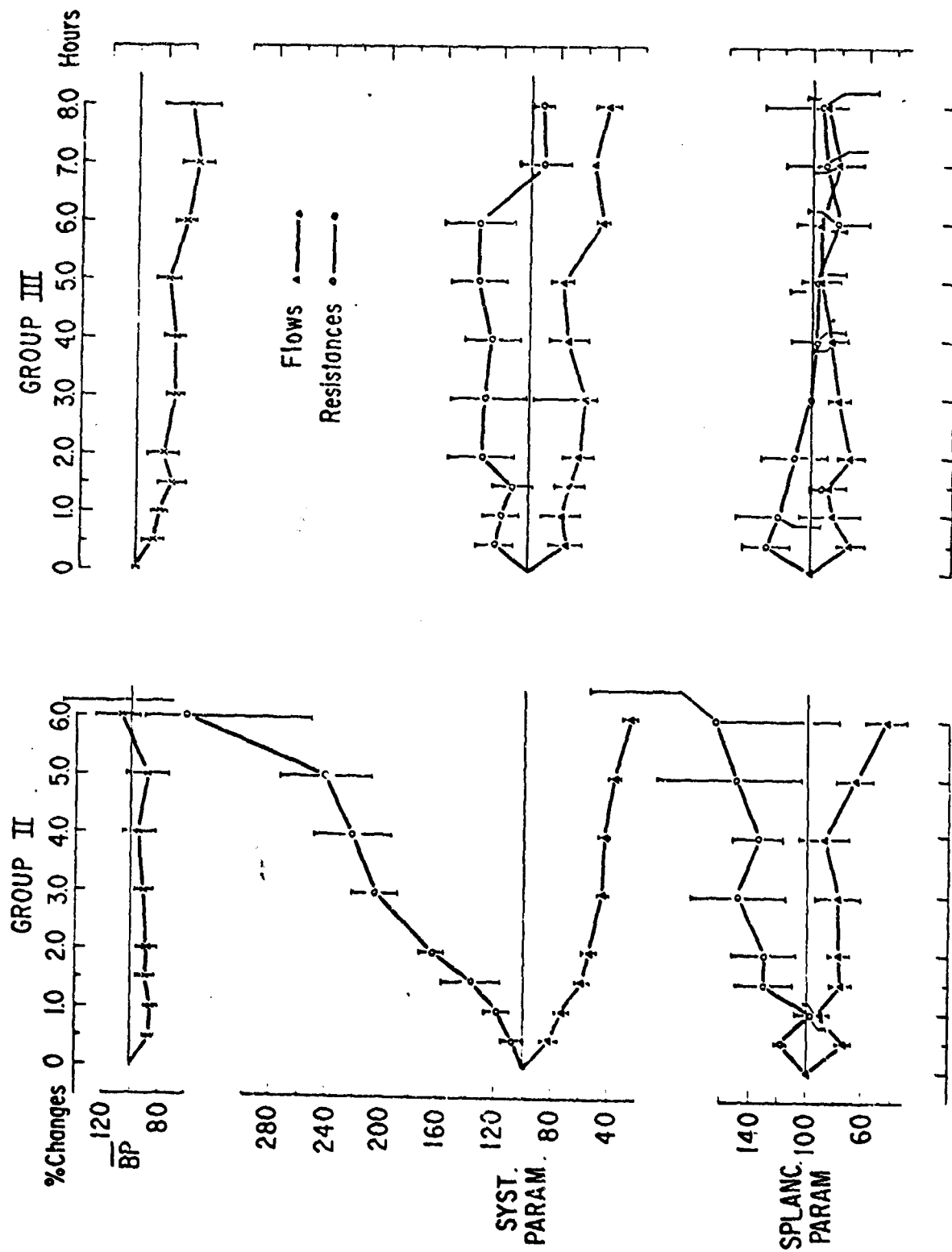
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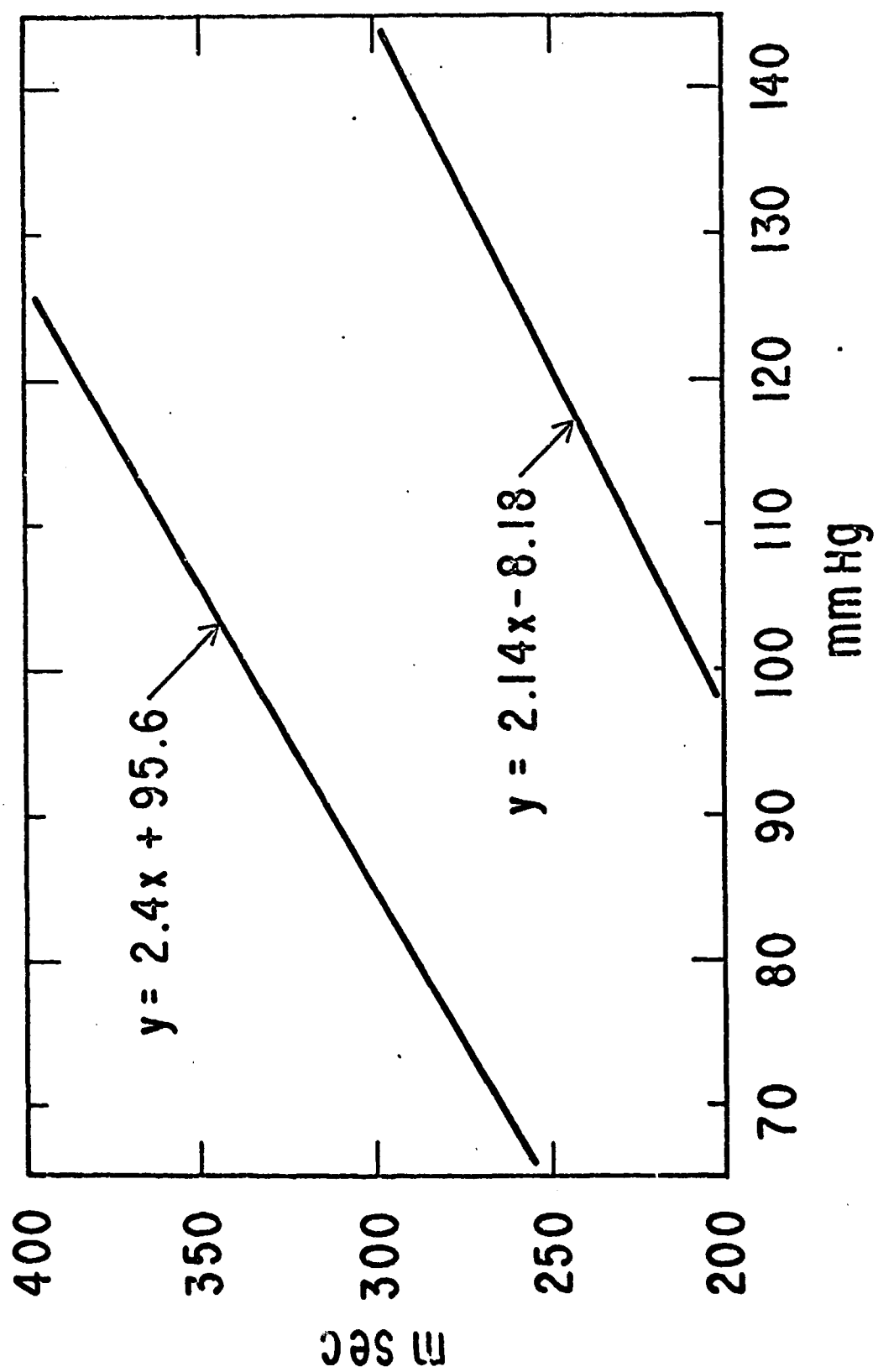HEMODYNAMIC CHANGES IN NON-ANESTHETIZED RABBITS

Figure 4.

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Figure 5.

baroreceptor sensitivity index in rabbits which succumbed 3 1/2 hours post-endotoxin. It can be seen that up to about 30 minutes before death, the baroreceptors were more sensitive than under controlled conditions. The lower part of the figure shows a representative protocol of a rabbit which survived for 10 hours post-endotoxin. Blood pressure throughout most of the syndrome fell to about 15 to 20% below control levels. In these animals the baroreceptor reflex showed an opposite trend, a continuous decline in sensitivity.

The following conclusions may be drawn: (A) anesthesia by itself serves to suppress some of the compensatory mechanisms which are observed in chronic non-anesthetized animals. (B) In the non-anesthetized group, two different patterns of response were observed - a protracted and hyperreactive sympathomimetic response with a comparatively short survival time; and a less pronounced sympathomimetic response with a significantly longer survival time. Paradoxically, it would appear that under conditions of reduced peripheral blood flow, the suppression or blunting of compensatory mechanisms actually enhances survival time. Our preliminary results based on a baroreceptor sensitivity test support such a conclusion.
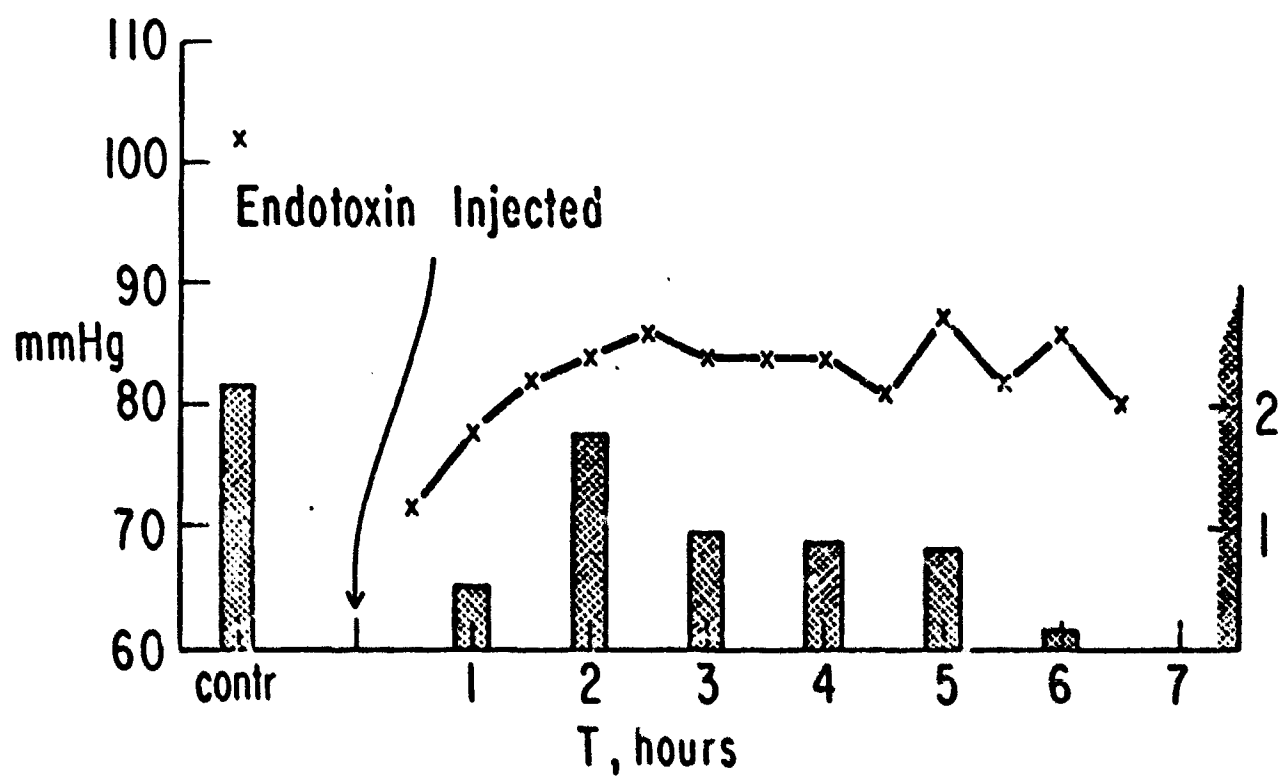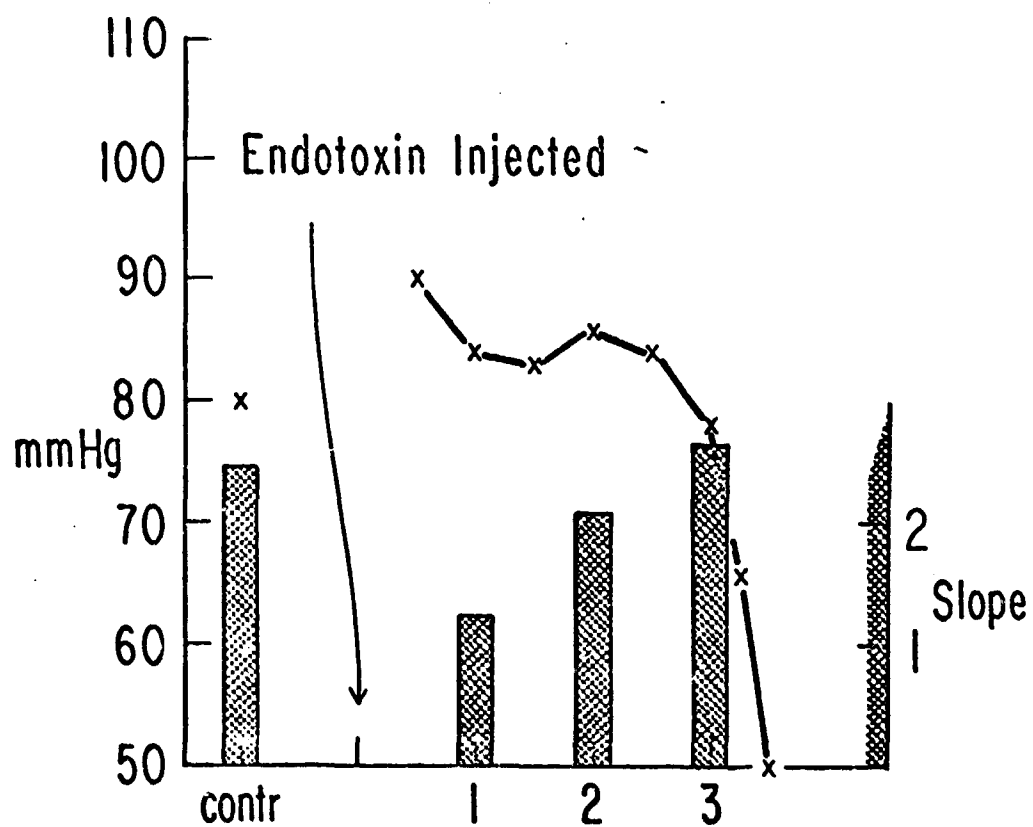
Figure 6.

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3.   Micro Pressures During Hemorrhagic Shock.

When pressure relationships within the splanchnic microcirculation following hemorrhage are determined directly with fine micro-probes, it can be seen that P_c (average capillary pressure) remains essentially unchanged until central arterial pressure falls to 45 mm Hg or below. Thus, despite extensive constriction of the larger blood vessels, readjustments of pre- and post-capillary resistance ratios permit tissue perfusion to be maintained at near normal levels. This capacity to autoregulate is progressively lost if the hypotension is protracted.

Continuous recording of central and microvascular pre- and post-capillary pressures bring to light a number of important adjustments which occur during the progression of the syndrome towards a lethal outcome.

As an example, Table I shows a representative protocol of the vascular events during fatal hemorrhage in the cat. It should be pointed out that the cat normally has a higher arterial pressure than other laboratory animals. As a consequence, capillary pressure (P_c) and plasma colloid osmotic pressure ($P\ell_\pi$) are atypical and high in this animal. Arteriolar pressure (P_a) falls quickly with even moderate blood loss (0-5% body wt.). Additional bleedings lower central blood pressure, but have little effect on P_a until $\overline{BP}$ falls below 40 mm Hg. Venular pressure (P_v) tends to fall proportionately less than P_a so that with more profound hypotension the pressure drop across the capillary bed proper is drastically reduced. The effects of such a narrowing of the pressure differential across the capillary bed are reflected in a markedly slowed blood flow through the capillary network, a reversal of flow in some vessels and a bypassing of still others. Clearly blood-tissue exchange is seriously disrupted.

When blood replacement measures are instituted after an extended

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TABLE I.

MICROVASCULAR ADJUSTMENTS FOLLOWING HEMORRHAGE
IN CAT MESENTERY

Condition	$\overline{BP}$ (Carotid) (mm Hg)	P_a (Arteriole) (mm Hg)	P_c (C. O. P.) (mm Hg)	P_v (Venule) (mm Hg)
Control	130	37	34	31
Bleeding #1 [*]	118	32	29	26
#2	82	24	21	19
#3	44	16	17. 5	13
#4	49	17	16	15
#5	22	9	8. 5	8
One hr. later	24	11	10. 5	10
Two hrs. later	28	11	10. 8	10. 7

[*] Bleedings carried out over a one hour period.

period of hypotension, a number of different patterns were observed. Pressures in the splanchnic capillary bed may fall to as low as 8-10 mm Hg during the terminal, decompensatory phase of the hemorrhagic shock syndrome.

The use of heparinized blood as a replacement measure, serves at first to improve capillary flow throughout the microcirculation. However, capillary pressure is found to be somewhat higher (by 5-6 mm Hg) than under control conditions, presumably because of precapillary dilation. In the type of preparation which becomes refractory to blood replacement, after a period of several hours, the purely mechanical effects of the elevated arterial pressure begin to wear off after 30-40 minutes. Failure of the circulation is preceded by a slowing of blood flow in the venules, thereby increasing outflow resistance as manifest by a jump in capillary pressure to about 30-35 mm Hg. Venular stasis then develops and in turn leads to a retrograde impairment of flow in the capillary tributaries, which likewise begin to develop areas of complete stasis. A number of factors are involved, including increased shear rate, elevated hematocrit (fluid loss during passage), a markedly reduced vis a tergo (pressure in collecting venules may fall as low as 8-10 cms. H_2O). These combine to dam up blood in the venular collecting system and to sequester blood needed to maintain venous return to the heart. Under these conditions, only a small percentage of capillaries which arise higher up on the arterial tree continue to exhibit an active blood flow, and capillary pressure falls to its lowest levels (below 10 mm Hg).

In some cases, where electrolyte solutions were used as cell free replacement fluids, the animals succumbed. In these instances the hematocrit falls to below 25 percent and the active circulation tends to bypass many of the capillaries. Thus, despite near normal pressures in these treated animals, only a portion of the network is perfused with blood.

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4. Fluid Exchange Mechanisms in Shock.

Fluid exchange across the blood capillary barrier depends upon the interplay of hydrostatic and colloid osmotic pressures of the blood, the permeability properties of the barrier per se (the so-called filtration coefficient), and the surface area available for exchange. In a dynamic context, an important feature of net fluid exchange for a particular vascular bed can be represented by a hypothetical cross-over point, which indicates the region in the capillary bed where hydrostatic and osmotic pressures are equal. On one side of the cross-over filtration would predominate, on the other absorption. Depending on the prevailing capillary pressure and the plasma colloid osmotic pressure, the cross-over could occur on the arterial, the mid-capillary or the venous side of the bed.

It should be noted that unlike the control situation where capillary pressure and plasma colloid osmotic pressures are matched within several mm Hg of one another, during shock these two forces become unbalanced. The accompanying figure (#7) illustrates the extent to which blood-tissue fluid exchange is disturbed on the basis of the Starling relationships between hydrostatic and colloid osmotic pressure during the successive phases of shock.

During stage (1), with the fall in hydrostatic pressure and arteriolar constriction, the cross-over point is shifted from the normal mid-line towards the arterioles. This provides a larger surface area to the right for absorption of fluid. As hemodilution occurs and $P\ell_\pi$ decreases, P_c again begins to predominate and the cross-over point shifts towards the venous side (Stage 2). With protracted hypotension, and a fall in driving pressure in the capillary bed, venous resistance increases. P_c is shifted upwards relative to the continued low levels of $P\ell_\pi$. Filtration is increased considerably and with the cross-over point shifted into the venules (Stage 3). Stasis begins to develop

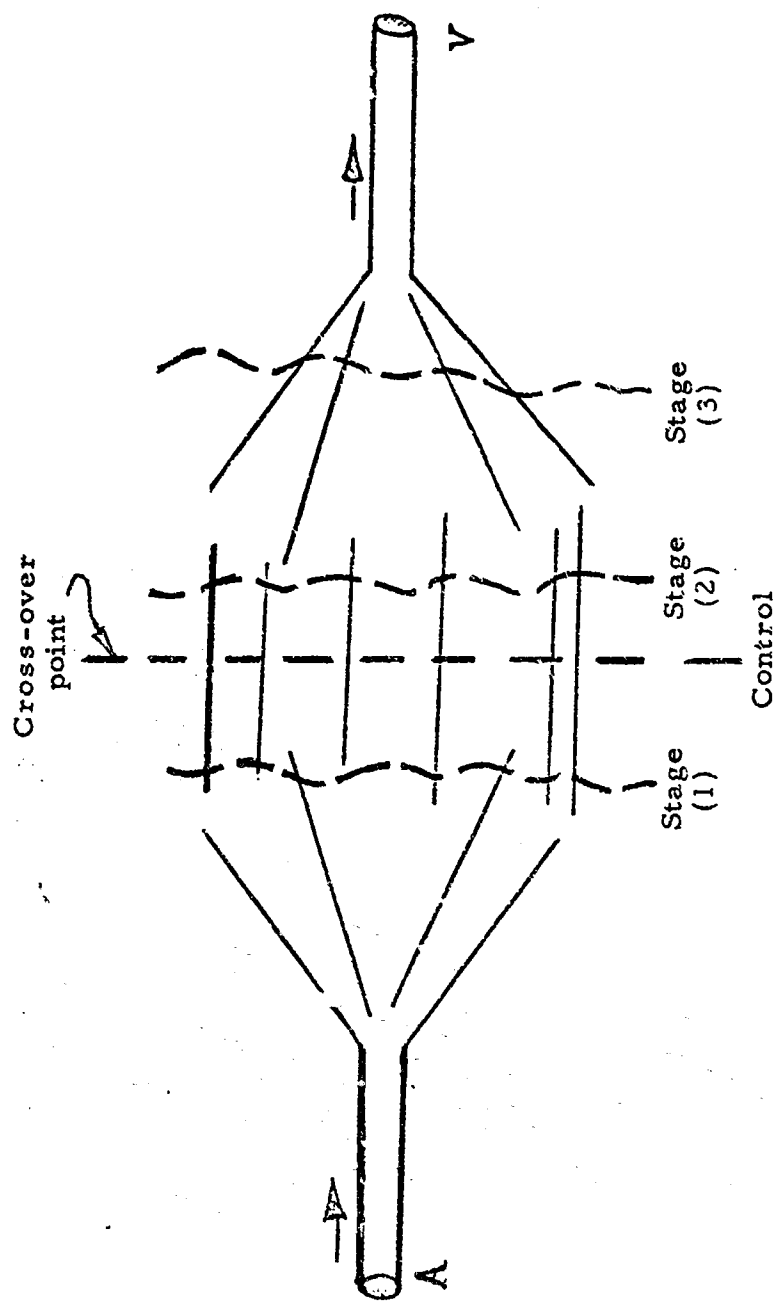22

SHIFT IN STARLING RELATIONSHIP FOLLOWING HEMORRHAGE

Figure 7.

and microcirculatory homeostasis is no longer possible.

A comparison was made of the effectiveness of two types of fluid therapy, blood and Ringer-Lactate, using locally operative factors such as $P\ell_{\pi}$, P_c, and the capillary permeability coefficient as a guide (rabbit and dog). We were especially interested in the prevailing capillary pressure (P_c) relative to the shifting level of plasma c.o.p. ($P\ell_{\pi}$) because of the key importance of these two factors in blood-tissue regulation of fluid exchange.

When hemorrhage was moderate (below 2% of body wt.) and of reasonably short duration (less than 3 hours), vascular permeability, as reflected by the filtration coefficient K, remains unchanged. Under these conditions a fall in $P\ell_{\pi}$ of as much as 40% below normal can be tolerated. When Ringer-Lactate was used as volume replacement, $P\ell_{\pi}$ fell to levels 65 to 75% below normal, and yet the animals recovered. Capillary pressure (P_c) remained comparatively low, possibly because of the decreased viscosity of the diluted blood and the decreased venous resistance.

Blood replacement following protracted hypotension, so-called irreversible shock, frequently did not restore capillary flow throughout the bed. Ringer-Lactate infusions at this stage were more successful in mechanically restoring capillary blood flow, but the effect was short lived and venular stasis developed. Presumably the blood capillary barrier has begun to deteriorate (K values may increase 2-3 fold) and fluid loss from the capillary network is excessive. As a basis of comparison, during moderate local inflammation, K values are increased about ten fold.

Irrespective of whether blood or Ringer-Lactate was used, the irreversible phase of the syndrome is characterized by considerable fluctuations in P_c. As flow slowed on the venular side, P_c rose to near arteriolar levels. This feature tended to increase venular flow but also produced a tendency for stasis

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in the collecting venules. Micro-thrombi or red cell aggregates were not seen. Stasis was the result of an increased P_c in the face of a low $P\ell_\pi$, especially noticeable in the venules.

SUMMARY STATEMENT

1.   The present studies demonstrate the usefulness of routine measurements of plasma c. o. p. both as a prognostic index of the course of the shock syndrome and as a guide for the effectiveness of other therapeutic measures.

2.   Severe and protracted hemorrhagic shock is associated with a failure of hemodilution mechanisms and a trend for $P\ell_\pi$ and blood hematocrit to become dissociated.

3.   Endotoxin has a clear cut action on neurogenic readjustment mechanisms which is masked in anesthetized animals.

4.   Survivors of an LD/50 dose of endotoxin, show a blunting of compensatory constrictor responses and thereby permit peripheral blood flow to be maintained more effectively as cardiac output and central pressure fall.

5.   Measurements of pressure within the microcirculation reveal that fatal shock is associated with an inability to maintain P_c and a progressive narrowing of the pressure differential or hydraulic driving force across the capillary bed.

6.   Fluid exchange at the capillary level is disrupted when P_c and $P\ell_\pi$ are no longer in balance and lead to extensive venular stasis during shock.

7.   Electrolyte therapy in hemorrhagic shock becomes less effective as the capillary barrier begins to show evidence of increased permeability (filtration coefficients may increase 2 to 3 fold).

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List of Relevant Publications (1970 - 1971).

1. Marty, A. T. and B. W. Zweifach. The high oncotic effects of Dextrans. Arch. of Surg., 101:421-424, 1970. (September)

2. Marty, A. T. and B. W. Zweifach. The splanchnic contribution to trans-capillary refill after hemorrhagic shock. (Submitted to Annals of Surgery).

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